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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,709	07/12/2001	Karine Vidal	113308-002	4054

7590 05/30/2003

Robert M Barrett
Bell Boyd & Lloyd
P O Box 1135
Chicago, IL 60690-1135

EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary	Application No.	Applicant(s)	
	09/807,709	VIDAL ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20-22 and 24* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group III (claims 18-24) in Paper No.11, filed on 17 March 2003 is acknowledged. Applicants have canceled claims 19 and 23. It is noted that Applicants reserve the right to amend the present application to add claims directed to the subject matter defined in claims 19 and 23.

Applicants request that upon allowance of the invention of linking claim 18, they should be allowed to reinstate species of GI tract disorders, recited in canceled claims 19 and 23. In the event where the invention recited in claim 18 is found allowable, claims that depend to claim 18, which recite GI disorder species, will be rejoined, so long as the claims do not precipitate new grounds of rejections.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-18, 20-22 and 24 are pending. Claims 18, 20-22 and 24 are drawn to the elected invention, thus, these claims will be searched and examined. Claims 1-17 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

Sequence compliance:

2. Applicants have submitted a computer readable form (CRF) and a paper copy of the sequence listing on 17 March 2003 in Paper NO:11. However, the submitted CRF was damaged and could not be read. It is requested that Applicants resubmit the computer readable form of the sequence listing when responding to this office action.

Claim rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 18, 20-22, 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention

Instant claims are drawn to a method of treating or preventing a GI tract disorder by administering an effective amount of a CD14 variant or fragment thereof which retains the bioactivity of CD14. Applicants assert that their invention is based upon the finding that mature milk comprises an unknown variant of CD14, which has high homology at the amino acid sequence level with serum soluble CD14, but has a different glycosylation pattern with regard to known forms of sCD14, (see page 6, lines 17-30). The specification refers the CD14 used in the method of the instant invention as mmsCD14 (mature milk soluble CD14) and discloses that this form of sCD14 has only N-glyocsylation and has no O-glycosylation, (see page 7, lines 5-19). The specification discloses that mmsCD14 stimulates the release of IL-8 by undifferentiated HT29 cells after a 24 hour incubation with 100 ng/ml *E.coli* LPS , (page 8, line 6-29).

Although the instant claims are drawn to a method of treating a GI tract disorder with a novel variant of CD14, isolated from mature milk, the specification does not

provide a written description for said variant. The specification discloses that the amino acid sequence including *N* and *C* terminus of the mature milk derived CD14 is *substantially* identical to that of serum soluble CD14, (see page 7, lines 5-7), however, the amino acid sequence of the mature milk variant CD14 is not disclosed in the instant specification. Therefore, it is not clear how much homology does the new CD14 variant share with the known soluble CD14. The specification does not disclose enough identifying structural characteristics about the variant of CD14 from mature milk used in the instantly claimed method, to satisfy the written description provision, under 35 U.S.C. 112, first paragraph. With respect to claims 21 and 22, instant specification does not define the structure of a variant or a fragment of CD14 that shares at least 70% homology to the amino acid sequence of human serum CD14, to be used in the instantly claimed method. The skilled artisan would not be able to visualize the structure of a variant or a fragment of CD14 that is substantially identical or that has at least 70% identity to the serum soluble CD14, because there is no disclosure of the amino acid sequence of the said variant or fragment. Furthermore, instant specification does not disclose where the similarities and the differences between the variant and the serum CD14 are found.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Therefore, the structure of the variant or fragment of CD14 used in the claimed method has not been disclosed on the instant specification, to satisfy the written description provision of 35 U.S.C. 112, first paragraph. As a result, it does not appear that the inventors were in possession of a variant or fragment of CD14 to be used in the claimed method.

3b. Claims 18, 20 -24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims are drawn to a method of treating or preventing a GI disorder by administering an effective amount of a CD14 variant or fragment thereof which retains the bioactivity of CD14. However, Applicants have not shown that the administration of a variant or fragment of CD14 treated or prevented any GI tract disorder. (GI tract is a long hollow tube stretching from the head to the end of the body, including the mouth, pharynx, stomach, small intestine, and large intestine. The salivary glands, liver, gallbladder, and pancreas are also important parts of this far-reaching system. Every section of the GI tract is prone to its own unique disorders--some potentially fatal. Therefore, the phrase "GI tract disorders" encompasses numerous and disparate disorders).

There is no data in the instant specification demonstrating that a variant or a fragment of CD14 treated or prevented any GI tract disorder. During the septic process, the barrier between the gastrointestinal (GI tract) and the blood stream becomes compromised causing endotoxin from bacteria in the GI tract to enter the blood stream. It is well documented in the relevant art that membrane bound CD14 serves as a high affinity receptor for LPS (polysaccharide found in gram-negative bacterial cell wall). In vitro studies have also shown that soluble CD14 mediates LPS-stimulated responses of cells lacking membrane CD14, (see Stelter et al, page 206, top of column 1). Stelter et al showed that while sCD14 has protective effect against lethality of mice that were injected with LPS, it had no protective effect on LPS-induced liver damage, (see Stelter et al, page 206, bottom of column 1 and page 211, column 2). Thus, while serum soluble CD14 might be considered as a potential therapeutic for gram-negative bacterial sepsis, Applicants have not demonstrated that the variant or fragment CD14 of the instant invention has any protective effect against any specific GI tract disorder, neither have they shown that said CD14 prevented any specific GI tract disorder. Furthermore, "prevention" means determining in advance if a patient is susceptible to a GI tract disorder and Applicants are not enabled for such.

With respect to claims 20 and 24, which further limit the claimed invention, to an infant formula comprising a variant or fragment of CD14 which retains the bioactivity of CD14, there is no disclosure in the instant specification of an infant formula which comprises a variant or fragment of CD14 that was used to treat or prevent a GI tract disorder. Examples 1-4 of the instant specification disclose the composition of different

infant formulas, however, Applicants have not shown that said infant formula was used to treat or prevent a GI tract disorder. There is no data regarding whether the infant formula disclosed in the instant specification is effective in the treatment or prevention of any GI tract disorder.

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, the amount of experimentation to test "all" possible variants and fragments of CD14 in their ability to treat or prevent "all" possible GI tract disorders, is undue, and there is no guidance provided by Applicants. Furthermore, the skilled artisan would not be able to predict if an infant formula comprising a CD14 variant or fragment would be effective in the treatment or prevention of GI tract disorder, given that there is no guidance in the instant specification regarding this issue. Therefore, Applicants are not enabled for the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 18, 20-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the claim is drawn to a method of treatment or prevention by administering a CD14 variant or fragment, however, the claim does recite who should the CD14 variant or fragment be administered to, and what should the result be after said administration?

4b. Claims 18, 20 and 24 are indefinite because the claims recite "..... which retains the bioactivity of CD14", however, it is unclear which "bioactivity" is being referred to? Appropriate correction is required.

4c. Claim 18 is also vague and indefinite for reciting "GI tract disorders", because it is unclear which diseases are encompassed by this phrase? The metes and bounds of the claim can be ascertained. Appropriate correction is required.

4d. Regarding claims 21 and 22, the phrase "including, include, includes" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The word "glycosylation" is misspelled in claim 22.

4e. Claim 21 recites "an amino acid sequence" in lines 2 and 3, however, it is unclear which amino acid sequence is being referred to. It is also unclear which amino acid

sequence of human serum CD14, should the CD14 variant or fragment to be used in the method of claim 21, share at least 70% homology?

According to 37 CFR 1.821 (d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Claim rejections-35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5a. Claim 18 is rejected under 35 U.S.C § 102(b) as being anticipated by Haziot et al (1995).

Haziot et al disclose a method of protecting mice from LPS-induced lethality, (see abstract). Using a mice sepsis model, the researchers injected C57BL/6J mice with LPS, followed by an injection of human recombinant soluble CD14(rsCD14), either immediately of after 10 minutes, (see page 6530, bottom of column 2). Haziot et al showed that 12ug/gbw of rsCD14 given immediately after LPS challenge or 10 minutes later significantly reduced mortality in mice, (page 6531, column 1 and figure 2).

It would be an inherent property of CD14 to treat GI tract disorder. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001) in which the Court found that preamble language in claims of patents directed to administration of anticancer drug are expressions of purposes and intended results, and

as such are non-limiting, since language does not result in manipulative difference in steps of claims.

It does not appear that claim 18 language or limitations result in a manipulative difference in the recited method when compared to the prior art disclosure.

The claimed process is not directed to a new use, it is the same use and it consists of the same method as described by Hiziot et al.

Therefore, Haziot et al reference anticipates instant claim 18 in the absence of any evidence to the contrary.

Conclusion

6. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday, Wednesday-Thursday, 6:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4227 for regular communications and (703) 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
May 30, 2003

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER